SUPPLEMENTARY MATERIAL

Journal: *Clinical Pharmacokinetics*

Pharmacokinetics and Pharmacodynamics of Prusogliptin (DBPR108), a Once-Daily Dipeptidyl Peptidase-4 Inhibitor, in Patients with Type 2 Diabetes

Wenfang Liu, Kexu Yang, Yang Lin, Chunyan Lu, Jingyi Liu, Huan Zhou, Juan Wang, Tianhao Zhang, Lingli Yao, Huanhuan Qi, Xiaofang Zhang, Rui Jia, Xiaoli Li, Shan Jing

Correspondence

Shan Jing, Clinical Pharmacology Center, Beijing Anzhen Hospital, Capital Medical University. E-mail: jingshan@anzhengcp.com.

Xiaoli Li, Clinical Trial Center, The First Affiliated Hospital of Bengbu Medical University. E-mail: 158169847@qq.com.

Eligibility Criteria

Inclusion Criteria:

1. Patients who met the World Health Organization (WHO) (1999) criteria for the diagnosis and classification criteria for type 2 diabetes mellitus;
2. 18 years ≤ age ≤ 75 years (inclusive), male or female;
3. 19 kg/m^2 ≤ body mass index ≤ 35 kg/m^2 (inclusive);
4. 7.0% ≤ glycosylated hemoglobin ≤ 9.5%;
5. Patients who voluntarily participated in the study and signed the informed consent form;
6. Patients who agreed to use contraception from the signing of the informed consent form to 1 month after the last administration of the study drug.

Exclusion Criteria:

1. Fasting plasma glucose > 13.9 mmol/L;
2. The patients needed to receive insulin therapy per the investigator's judgement;
3. Patients had acute or serious complications of diabetes (including diabetic ketoacidosis, hyperosmotic nonketotic diabetic coma, lactic acidosis, and hypoglycemia coma);
4. History of severe hypoglycemia (hypoglycemia with severe cognitive impairment and requiring other measures to help recover);
5. History of acute or chronic pancreatitis, or related diseases that were common cause of acute pancreatitis (such as cholelithiasis, etc.);
6. History of allergy to DPP-4 inhibitors or the patients could be allergic to study drug per the investigator's judgement;
7. Patients had untreated hyperthyroidism or other diseases that might affect blood glucose;
8. Patients who had used other hypoglycemic drugs within 14 days before the first dose of study drug; or patients who were not suitable for this study as determined by the investigator due to taking other hypoglycemic drugs;

9. Patients had inflammatory bowel disease, partial intestinal obstruction, or chronic bowel disease related to obvious digestive and absorption disorders;
10. Aspartate aminotransferase or alanine aminotransferase > 3 × upper limit of normal (ULN), or total bilirubin > 1.5 × ULN;
11. Abnormal renal function: serum creatinine > 1.5 × ULN; or estimated Glomerular filtration rate < 45 mL/min/1.73m^2;
12. White blood cells (WBC) < 3.0 × 10^9/L and neutrophil count of peripheral blood < 1.5 × 10^9/L; hemoglobin < 100 g/L; triglyceride > 5.7 mmol/L;
13. Patients who had the second or third degree atrioventricular block, long Q-T syndrome, or corrected QT interval> 500 ms without cardiac pacemaker;
14. Patients had positive test result for any of the following: hepatitis B surface antigen, hepatitis C antibody, anti-HIV antibody, or antibody of treponema pallidum positive;
15. Female patients of childbearing age with pregnancy test positive or lactating women;
16. Patient had history of alcohol or drug abuse within 3 months before screening. Alcohol abuse was defined as average alcohol intake more than 14 units alcohol (1 unit = 12 ounces or 360 mL of beer, 1.5 ounces or 45 mL spirits with 40% alcohol/volume, 5 ounces or 150 mL grape wine); or consumed any other products containing alcohol within 2 days before the first administration of study drug;
17. Patients who smoked > 5 cigarettes/day within 3 months prior to screening;
18. Patients who consumed grapefruit juice, methylxanthine-rich food or beverage (such as coffee, tea, cola, chocolate, energy drinks) within 2 days before the first administration of study drug during treatment period; had strenuous exercise; or had other factors affecting drug absorption, distribution, metabolism, excretion;
19. Participation in other clinical trials or administration of any other investigational drugs or devices within 3 months before screening;

20. Patients with the following diseases:

a) Serious dysrhythmias, obvious left ventricular dysfunction, New York Heart Association functional class III or IV;

b) History of unstable angina pectoris, myocardial infarction, or other high-risk coronary artery diseases;

c) Uncontrolled hypertension, systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg;

d) History of cancer or organ transplantation;

e) History of epilepsy, psychosis, or severe depression, etc.

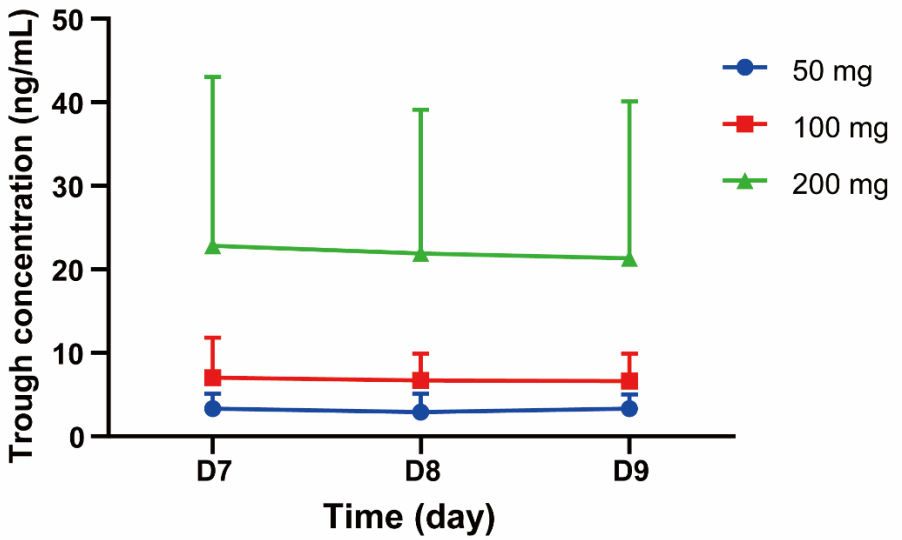
21. Not suitable for this study as determined by the investigator due to other reasons.

Table 1 Analysis of dose proportionality of DBPR108 based on power model (PKPS)

PK parameter	*N*	Slope (90% CI)	Intercept (90% CI)
Single dose of DBPR108			
C_{max} (ng/mL)	30	0.85 (0.62, 1.09)	1.56 (0.44, 2.67)
AUC_{last} (h×ng/mL)	30	1.02 (0.86, 1.18)	2.60 (1.87, 3.34)
AUC_{inf} (h×ng/mL)	30	1.04 (0.87, 1.21)	2.57 (1.80, 3.35)
Multiple doses of DBPR108			
$C_{max,ss}$ (ng/mL)	30	1.08 (0.84, 1.32)	0.48 (–0.59, 1.55)
$AUC_{tau,ss}$ (h×ng/mL)	30	1.11 (0.93, 1.30)	2.14 (1.27, 3.01)
$AUC_{inf,ss}$ (h×ng/mL)	30	1.15 (0.95, 1.36)	2.05 (1.10, 3.00)
$AUC_{last,ss}$ (h×ng/mL)	30	1.16 (0.97, 1.37)	1.95 (1.02, 2.89)

AUC area under the plasma concentration–time curve, AUC_{inf} AUC from time zero to infinity, $AUC_{inf,ss}$ AUC from time zero to infinity at steady state, AUC_{last} AUC from time zero to the time of the last measurable concentration, $AUC_{last,ss}$ AUC from time zero to the time of the last measurable concentration at steady state, $AUC_{tau,ss}$ AUC during a dosage interval at steady state, C_{max} maximum plasma drug concentration, $C_{max,ss}$ maximum plasma drug concentration at steady state, *PKPS* pharmacokinetics parameter set.

Figure 1 Trough concentration of DBPR108 (PKCS)



PKCS, pharmacokinetics concentration set.